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Therapeutic drug monitoring of atypical antipsychotics

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Summary

The paper presents an overview and analysis of the results of research on therapeutic ranges of concentrations and receptor occupancy, mainly D2 receptors, in the treatment with some atypical antipsychotic drugs. Amisulpride, aripiprazole, clozapine, quetiapine, olanzapine, risperidone, paliperidone, sertindole, and ziprasidone were taken into account. The benefits of therapeutic drug monitoring to optimize the effectiveness of treatment and avoid side effects or toxicity were shown. The safety of patients, with the possibility to use the lowest effective dose, is an undoubted profit of TDM. This helps to avoid overdosing resulting in adverse events (with particular emphasis on extrapyramidal symptoms and seizures). The need and desirability of TDM is due to the inter – and intraindividual differences in the pharmacokinetics of drugs, because only some of them have a close correlation between dose and plasma concentration. The plasma concentration correlates well with the occupancy of D2 receptors. The efficient and safe level is determined at 60–80%. Based on the knowledge of the indications for TDM and therapeutic concentration ranges, amisulpride, clozapine and olanzapine have the highest level of recommendation to use TDM. Therapeutic ranges of plasma concentrations of the analyzed drugs were determined to be 200–320 ng/ml for amisulpride, 150–210 ng/ml for aripiprazole, over 350–500 ng/ml for clozapine, 50–500 ng/ml for quetiapine, 20–40 ng/ml for olanzapine, 20–60 ng/ml for risperidone and paliperidone, 50–100 ng/ml for sertindole and 50–130 ng/ml for ziprasidone.

Key words: therapeutic drug monitoring, plasma concentration, atypical antipsychotics

Introduction

Therapeutic Drug Monitoring (TDM) makes it possible to respond to individual differences disclosed in the course of treatment through proper interpretation of clinical and laboratory findings. It gives a chance to avoid adverse effects, toxicity or lack of efficacy. Such optimization is intended to reduce the cost of treatment with an increase of the safety of the patient.

TDM in psychiatry has been a subject of discussion and a lot of research because specific guidelines have been developed only for a few drugs, such as mood

stabilizers (lithium, valproate, carbamazepine), some antidepressants and several antipsychotics.

In response to the therapeutic problems in clinical trials, guidelines for the use of TDM in the treatment of mental disorders have been developed by a group of German experts – AGNP (*Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie*) [1]. The guidelines are presented in Table 1.

Table 1. **Indications for the use of therapeutic drug monitoring in the treatment of mental disorders (AGNP)**

Clinical situations in which TDM is justified:
Suspected non-adherence
Drugs for which TDM is mandatory for safety reasons (e.g., lithium)
Narrow therapeutic range
Non-linear dose-concentration ratio
Lack of clinical response, or insufficient response even if doses are considered as adequate
Adverse effects despite the use of therapeutic doses
Suspected drug interactions
TDM in pharmacovigilance programs
Combination treatment with a drug known for its interaction potential, in situations of comorbidities, augmentation
Relapse prevention in long-term treatments, prophylactic treatments
Recurrence despite good compliance and adequate doses
Presence of a genetic particularity concerning the drug metabolism
Children, adolescents and elderly patients (>65 years)
Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
Forensic psychiatry
Problems occurring after switching from an original preparation to a generic form (and vice versa)

TDM uses a number of new, innovative methods of measuring the plasma concentrations of drugs. High-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC) are the most recommended and described techniques for measuring the concentrations of drugs and their active metabolites separately. Immunochemical methods: EIA (enzyme immunoassay), FPIA (fluorescence polarization immunoassay) and ELISA (enzyme-linked immunosorbent assay) are characterized by high sensitivity and speed of measurement. New analytical methods, for example, capillary electrophoresis (CE) are also used. PET (positron emission tomography) and SPECT (single-photon emission computed tomography) are used to assess the degree of receptor occupancy (in the case of antipsychotic drugs – mainly dopamine D2 receptors), which can be an important indicator of treatment efficacy together with the plasma concentrations.

This work presents an overview of the results of research carried out for determining therapeutic ranges of plasma concentrations of some atypical antipsychotics to optimize therapy.

Amisulpride

Amisulpride is an antipsychotic drug of the benzamide group. Its half-life is 12–20 hours. Only approximately 4% of the administered dose is metabolized in the liver to 2 inactive metabolites. The average therapeutic dose range is 300–800 mg/day.

The plasma concentrations of amisulpride were the subject of many studies, including German ones. Differences depending on age and gender were observed [2–4]. In a study of 395 patients treated with amisulpride (dose of 574 (+/ – 269) mg/day), higher concentrations have been demonstrated in women than in men. Average plasma concentration was 304 (+/ – 274) ng/ml. In people over 60 years of age, higher plasma concentrations were observed at comparable doses [2]. In another study, involving 99 patients treated with amisulpride as monotherapy (doses higher or equal to 400 mg/day), higher levels in women were also observed. However, this had no significant impact on the clinical response (respectively 77 and 79%) and adverse events (41 and 37%) [3]. Similar results were obtained in a study by Bergemann et al. [4] on a group of 85 patients. Other groups were also observed: smokers (no effect on the plasma concentrations of amisulpride) and patients concomitantly taking other medications: lithium, clozapine (increased plasma levels), benzodiazepines, and classical antipsychotics (no effect). The study conducted by Müller et al. [5] on 378 patients treated with daily doses of 100–1,550 mg of amisulpride (an average of 594 mg/day) showed a direct relationship of the plasma concentration and the dose. Only in patients with insufficient clinical response, the concentrations were much lower. On the contrary, patients achieving higher concentrations of the drug reported the occurrence of side effects, particularly extrapyramidal symptoms (14.6% of respondents). It was determined that the concentrations providing clinical response and no adverse effects should be within the range of 100–320 ng/ml.

The literature analyzing the conducted studies suggests respectively: amisulpride daily dose of 400–800 mg, plasma concentration of 200–500 ng/ml and safe levels (to avoid the extrapyramidal symptoms) within the range of **200–320 ng/ml** [6]. It is suspected that the lower D2 receptor occupancy in the striatum (compared with the thalamus and temporal cortex) may account for a low risk of extrapyramidal symptoms, and preferential occupancy of the limbic system – therapeutic efficacy [7, 8].

However the dependence of plasma levels on dosage is proportional in most patients, a small percentage of non-response to treatment, concomitant use of other drugs, the patient's age, and even diet (carbohydrates shorten the time to reach maximum concentration at its generally lower value) can be indications for the need to monitor the plasma concentrations of amisulpride.

Aripiprazole

Aripiprazole belongs to the group of quinolinone derivatives. Aripiprazole is metabolized in the liver by CYP3A4 and CYP2D6 to its active metabolite – dehydroaripiprazole (DARI). The half-life of aripiprazole is different depending on the activity of CYP2D6, within the range of 60–146 hours, and of DARI – approximately 94 hours. In Polish literature, the recommended dose range is 15–30 mg/day. In British studies, the highest proportion of therapeutic response was achieved at a dose of 10 mg/day [9], without significant benefits of doses above 20 mg/day [10].

In several studies by Kirschbaum et al., plasma levels of the parent compound and the active metabolite were evaluated at a dose of 20 (+/-8) mg/day and 10–30 mg/day (in each case median of 15 mg/day). The obtained results were similar, at the average level of 146–254 ng/ml [11] and 150–300 ng/ml [12], without significant side effects in the range of 110–249 ng/ml [12]. In literature analyzing the studies, the safe and effective plasma concentration of aripiprazole is suggested to be in the range of **150-210 ng/ml** [9]. In most patients, the relationship between dose and the achieved concentration is proportional. It should be noted that even at a concentration of 5–10 ng/ml, the D2 and D3 receptor occupancy reaches 50% of the maximum saturation, and above 100–150 ng/ml – achieves total saturation [13]. In other studies the concentrations achieved by patients of different age, sex, BMI, having different smoking habits, and taking other medicines (such as fluoxetine, paroxetine) were compared. There were no significant effects of these factors on the plasma concentrations of aripiprazole [14, 15]. Significant differences were expressed in patients with different CYP2D6 genotype who metabolize the drug to a variable extent and reach similar concentrations at doses that differ up to 40% [16].

Considering the above, in the majority of patients therapeutic drug monitoring of aripiprazole is not justified. However, it may be helpful in cases of questionable cooperation and genotypic differences.

Clozapine

Clozapine is a dibenzodiazepine derivative. It is the most efficacious antipsychotic drug in drug-resistant patients. It has one of the most complex receptor mechanisms. Its half-life is 6–26 hours, 12 on average. It is almost completely metabolized, primarily with the involvement of CYP1A2, CYP3A4 and CYP2D6. The average therapeutic dose is in the range of 200–600 mg/day.

In the case of clozapine, the dose and plasma concentration are related linearly [17, 18]. However, concentrations achieved on a given dose depend on many factors. In a study by Haring et al. on 148 patients taking a wide range of daily doses (12.5–700 mg), percentage differences in several groups were evaluated. The researchers observed higher concentrations in women in relation to men – 100:69.3%, in non-smoking men compared to the smoking ones – 100:81.8% (in women there was no significant difference) and in older patients compared to younger ones [18]. Another study evaluated the racial differences. Asians (Caucasian race) needed approximately

twice lower doses to achieve similar concentrations of the parent substance and metabolites [19]. Some substances affect the metabolism of clozapine by changing the activity of cytochrome, mainly CYP1A2 – for example carbamazepine, phenytoin and tobacco lower the concentration of clozapine through induction of the cytochrome, while inhibitors, such as erythromycin or caffeine – vice versa [20, 21].

Other relevant factors include inflammation-induced toxic concentration increases by raising the levels of proinflammatory cytokines and inhibition of CYP1A2 [22]. Similarly, respiratory infections with fever can cause even a double increase of clozapine concentrations [23]. Algorithms to evaluate the appropriate plasma concentration of the drug and its metabolites according to individual characteristics, such as gender, age, body weight, smoking habits, were developed [24]. However, the above-mentioned factors may be an obstacle to the use of such algorithms.

Taking into account the research from the 1990s, many researchers tried to determine the concentrations and therapeutic response thresholds for clozapine. The obtained results were different: 200 ng/ml [25], 350 ng/ml [26, 27], 370 ng/ml [28], 420 ng/ml [29], 504 ng/ml [30], and 550 ng/ml [31]. On average, **350–500 ng/ml** is given as the minimum concentration for therapeutic response, although the upper limit of the recommended concentrations has not been established. The concentration of 200 ng/ml was defined as threshold for relapse prevention in the treatment of schizophrenia [32], and large fluctuations of concentrations as an increased risk of relapse [33]. Concentrations above 250 ng/ml carry the risk of various side effects [34]. In 2 independent studies conducted by Greenwood-Smith and Varma et al., the concentrations of 1,000 ng/ml [35] and 1,300 ng/ml [36] were reported as significantly increasing the risk of seizures. Therefore, it is proposed to consider the administration of an anticonvulsant (valproate, lamotrigine) above a concentration of 500 ng/ml [36]. In case of hematological and cardiac disturbances, no close connection with the concentration of clozapine was indicated [35].

Therapeutic guidelines recommend monitoring of the concentration of clozapine, with a particular focus on weak response to treatment, the suspicion of non-cooperation, toxicity, the occurrence of significant adverse reactions (seizures), liver disease, or the effect of other medicines and stimulants. In these situations, the therapeutic drug monitoring of clozapine may have important clinical value.

Quetiapine

Quetiapine is a benzodiazepine derivative. It is metabolized in the liver through CYP3A4 to more than 20 metabolites. The half-life is about 7 hours. The average therapeutic dose in schizophrenia is in the range of 200–600 mg/day. Despite the tendency of many clinicians to increase doses even above 800 mg/day, studies have demonstrated that doses of quetiapine in the range of 150–450 mg/day are no less efficient than those up to 750 mg/day. In the case of extended-release quetiapine, the dose of 400 mg/day is also as effective as up to 800 mg/day [37].

The range of concentrations recommended for adults to exclude adverse effects is within **70–170 ng/ml** [38]. Other sources give a concentration range for the effective

treatment of schizophrenia at **50–500 ng/ml** [39]. Both the literature review and recent studies on children, adolescents and adults in which the relationship between doses, plasma concentrations, therapeutic response and the occurrence of adverse reactions were observed, reported a poor relationship between the dose and the concentration and no relationship between concentration and therapeutic response [38, 40, 41]. No differences in pharmacokinetics of quetiapine between children and adults were found [42, 43]. Only a relationship between the dose and D2 receptor occupancy [41] and preferential D2 receptor binding in the extrastriatal areas [44] was observed. Similar results were obtained in 80% of patients in mono – and polytherapy, significantly lower concentrations were obtained only in patients co-administered with carbamazepine [40]. It would therefore seem that the monitoring of quetiapine plasma concentrations does not apply to optimize the dosage.

In the 3-year study by Castberg et al. [45] on a group of 1,179 patients treated with quetiapine, the impact of age and other drugs on its pharmacokinetics was observed. It was found that age over 70 years affects the increase in concentration of quetiapine, while under 18 years of age – the other way around. Simultaneous administration of CYP3A4 inhibitors: alimemazine, citalopram, escitalopram, and, in particular, clozapine and fluvoxamine significantly increases the plasma concentration of quetiapine. Conversely, lamotrigine, levomepromazine, oxazepam, and carbamazepine cause the decrease of quetiapine plasma levels [45]. In a study conducted by Aichhorn et al. [46], the influence of age and sex on the increase of quetiapine concentrations was confirmed, with higher concentrations in women having no clinical significance. An exceptional increase in the concentration of quetiapine (77%) has been noticed with valproate co-administration. An additional factor is polymorphism of CYP3A4 among patients. CYP3A4*22 allele is responsible for an increase of quetiapine concentration [47]. In such cases, the usefulness of quetiapine therapeutic drug monitoring seems important.

Olanzapine

Olanzapine is derived from thienobenzodiazepine, and is an antagonist of serotonin and dopamine. It is metabolized in the liver in approximately 40% during the first pass, and the unchanged molecule shows the main pharmacological activity. Half-life in a young, healthy person is about 34 hours and increases with age, it is also longer in women and non-smokers. The average therapeutic dose is 10–20 mg/day.

In the study by Aravagiri et al. [48], it was found that the daily doses of 10, 15 or 20 mg are linearly related to the achieved plasma concentrations, ranging from 0.25 to 50 ng/ml. In other studies, the impact of age, gender, tobacco and other drugs on the concentration of olanzapine was evaluated in the same patients at different doses (proportional relationship) or in the same person and different people at a stable dose (a dispersion of approx. 30% and approx. 49%, respectively). In women and people over 60 years of age the concentrations were higher, in smokers and African-Americans – lower [49–52]. In a study by Nozawa et al. [53] age, sex and, in particular, smoking are listed as factors of a more significant impact on the olanzapine concentration than the genetic polymorphism of UGT1A4, CYP3A4 and CYP2D6. A positive impact

of fluvoxamine (+74%) and to a lesser extent: paroxetine, fluoxetine, sertraline, and venlafaxine was noticed, and negative – of P450 inducers [49, 54], lithium and trimipramine [55]. In comparison with monotherapy, amitriptyline, benperidol, flupentixol, and lorazepam had no impact on olanzapine concentrations [55]. In different studies, the influence of carbamazepine was indicated as neutral [55] or negative [52, 54]. Patients previously treated with clozapine presented higher plasma concentrations of olanzapine [50]. In studies involving patients with schizophrenia, a threshold for response to treatment (an improvement of at least 20% in the BPRS or the PANSS) was suggested at > 9 ng/ml [56] and 23 ng/ml at the time of 13.5 h after the dose [57]. In the study by Mauri et al., [58] no additional benefit was found at concentrations higher than 40 ng/ml. Therefore, a therapeutic concentration range of **20–40 ng/ml** has been suggested, while concentrations above 80 ng/ml can cause the occurrence of adverse effects [54]. Concentrations above 100 ng/ml are considered toxic, and above 160 ng/ml potentially fatal, especially when taking other medications [59]. Olanzapine is burdened with the risk of many adverse reactions, even in therapeutic ranges. One of the most important, hard-to-avoid effects, is clinically significant weight gain (>= 7%) observed even at levels of 20.6 ng/ml [60].

In some sources, large (up to 47%) interindividual differences in plasma concentrations of olanzapine are considered as limitation of TDM value [61]. Monitoring the concentration of olanzapine seems appropriate in cases in which non-adherence is suspected, when the maximum recommended daily dose gives no expected therapeutic response (about 20% of patients do not achieve a concentration of 20 ng/ml at a dose of 20 mg/day [62]) or the above-mentioned factors affecting the concentration of olanzapine are present.

Risperidone

Risperidone belongs to benzisoxazole derivatives. It is metabolized in the liver with the participation of CYP2D6 to an active metabolite – 9-hydroxyrisperidone and other inactive metabolites. After oral administration, the half-life is 3 hours for risperidone, and 23–24 hours for 9-hydroxyrisperidone. The minimum daily dose is 1 mg and the average therapeutic dose is in the range of 2–4 mg/day. No additional benefits from the application of doses above 8 mg/day have been demonstrated.

The therapeutic plasma concentration of risperidone shall be within the range of **20–60 ng/ml** (parent substance plus active metabolite) [63, 64]. In some studies, ranges of 25–150 ng/ml (therapeutic concentrations) and 25–80 ng/ml (optimum concentration – without side effects) have been suggested [65]. In the 6-week study by Lane et al. [66] with the participation of 30 patients, the dose of risperidone was titrated to 6 mg/day to observe the therapeutic response and side effects. As a result, 13 patients needed to reduce the dose to approximately 3 mg/day with similar plasma concentrations (on average: 40.4 ng/ml at reduced doses and 49.7 ng/ml at 6 mg/day) and still good therapeutic response. It seems that individual metabolism of the drug plays a vital role in achieving therapeutic concentrations. In another study using the BPRS, a positive correlation between the concentration of risperidone and im-

provement of positive symptoms and cognitive function in schizophrenia, and the concentration of the active moiety and improvement in depressive symptoms and anxiety was demonstrated. Both of these correlations resulted in total improvement in the BPRS. Both concentrations correlated linearly with the occurrence of adverse effects [67].

An important indicator of the efficacy of treatment is the D2 receptor occupancy, which should reach 65% for a minimal therapeutic effect [64]. In studies conducted by Nyberg et al. [68], the average D2 occupancy at an oral dose of 6 mg/day was 82% and extrapyramidal symptoms were observed in most patients. After the reduction of doses, a safe level of receptor occupancy within 70–80% and a dose of 4 mg/day were specified. Numerous studies on the effectiveness of the drug in the depot form at doses of 25, 50 and 75 mg/2 weeks were carried out. Various concentrations were achieved: 4.4–8.8 ng/ml [69] and even 22.7 ng/ml [70] at a dose of 25 mg/2 weeks, 15–31.1 ng/ml [69] at a dose of 50 mg/2 weeks and 22.5–26.3 [69] at a dose of 75 mg/2 weeks. At the same time, with the use of PET, the percentage of D2 receptor occupancy was determined at doses as above, reaching the results of 25–48%, 59–83%, 62–72%, respectively [69]. As a result, the dose of 25 mg/2 weeks gave a sub-clinical effect because D2 receptor occupancy did not reach a therapeutic threshold [69]. In general, patients receiving the drug in a depot form achieved lower concentrations of the sum of the parent substance and the active metabolite than those receiving the oral form. Therefore, monitoring the risperidone/9-OH-risperidone ratio [71] or receptor occupancy seems more reasonable.

Studies on the pharmacokinetics of risperidone and its metabolites depending on age, gender, body weight, smoking habits, co-administered drugs, and CYP2D6 genotype have been conducted. It was shown that there is a linear relationship between age and 9-OH-risperidone clearance [72] and the concentration of the active moiety [73]. The effect of CYP2D6 genotype on risperidone metabolites clearance, with comparable efficiency of treatment, was proven. Poor metabolizers achieved the concentrations of active moiety up to 3.3-fold higher at the same doses [74, 75]. Similarly, patients with parkinsonism or dystonia as well as chronic patients, achieved higher concentrations [74–76].

Monitoring levels of prolactin could be an effective indicator of the patient's cooperation. Regarding unequivocally determined relationship between doses, receptor occupancy levels and therapeutic plasma concentrations, monitoring of the latter would seem appropriate only in individual situations, for example, lack of therapeutic response, unexplained adverse effects or co-medication.

Paliperidone

Paliperidone (9-hydroxyrisperidone) is a hydroxyl derivative of risperidone, its active metabolite. Like risperidone, it is characterized by a smaller risk of extrapyramidal symptoms and motor disorders than typical antipsychotics. Half-life is approximately 23–24 hours. The average oral therapeutic dose is 3–12 mg/day, and for paliperidone palmitate administered intramuscularly in maintenance treatment – 75 mg/month.

The level of D2 receptors occupancy is important. In the 6-week study of patients with schizophrenia receiving daily doses of 3, 9 and 15 mg, the optimal range of doses was calculated based on PET measures (receptor occupancy in the striatum and in the temporal cortex) and the plasma concentrations of the drug. An optimal D2 receptor occupancy was found at the level of 70–80% at doses of 6–9 mg/day [77]. In 2012, in the study by Muly et al., D2 receptor occupancy was evaluated in different areas of the brain in macaques receiving risperidone and paliperidone, and compared with plasma and cerebrospinal fluid concentrations. The optimum plasma concentration range of 40–80 ng/ml for both substances was confirmed [78]. Somewhat lower concentration ranges (20–52 ng/ml) are proposed in the conclusions of the study conducted by Nazirizadeh et al. [79] on 217 patients receiving paliperidone alone, in which a significant clinical improvement was achieved in the CGI. In other reports, the therapeutic concentrations range of **20–60 ng/ml** is proposed [80] – the same as for risperidone. In paliperidone therapy, the relation between clinical improvement, risk of extrapyramidal symptoms, increased prolactin levels and plasma concentrations is not linear [81]. It has also been noticed that CYP2D6 polymorphism does not affect the plasma concentrations of the drug [82].

The literature highlights the potential usefulness of therapeutic drug monitoring of paliperidone. However, there is still relatively little research.

Sertindole

Sertindole is an antipsychotic drug with the selective antagonistic action on dopamine D2 receptors. Metabolism occurs in the liver, with the participation of CYP3A4 and CYP2D6. Sertindole and its metabolites (dehydrosertindole, norsertindole) are excreted slowly. Half-life is 55–90 hours and the average recommended therapeutic dose – 12–20 mg/day.

In the literature, few reports from research on this drug can be found. There are detailed descriptions of some methods used in them, such as dry blood spots, HPLC-UV, HPLC, or fluorimetric detection [83–85]. The studies were carried out on guinea pigs [86], rats [87, 88], and with the participation of people – on very small groups of patients (from 2 up to approx. 40 divided into groups). The research on sertindole shows several arrangements for its pharmacokinetics in different patients. There is no need for dose adjustment in patients with varying degrees of renal insufficiency [89]. QT prolongation occurs frequently as an adverse reaction of sertindole. The concentration of the drug in myocardium reaches a value of 3.1 times higher than in plasma (with values of more than 4-fold higher significantly increasing the risk of arrhythmia and sudden cardiac death) [86, 90]. In a study involving patients divided into four groups depending on sex and age, it has been demonstrated that age does not have a significant impact on plasma concentrations, while higher concentrations (by an average of 29%) at the same dose were observed in females [91].

It seems important that the antipsychotic effect of sertindole is not associated with a large D2 receptor occupancy in the striatum [92]. At a dose of 20 mg/day, 4 patients diagnosed with schizophrenia reached 52–68% occupancy of D2 receptors

in the striatum, as well as in the thalamus and the temporal and frontal cortex [93]. In another study, 2 patients reached D2 occupancy of 15 and 6% at a dose of 4 mg/day [94]. The relationship of the occurrence of extrapyramidal symptoms and lower D2 receptor occupancy in the case of sertindole in comparison with other antipsychotic drugs is debatable [93, 95]. Also, higher occupancy of 5HT2A receptor than D1 and D2 was found, which, in a long time, may be associated with a lower risk of extrapyramidal symptoms [88].

Few studies clearly define a target plasma concentration range for sertindole, giving priority to receptor occupancy. In a collective article by Hiemke et al. [96], a target therapeutic range is specified as **50–100 ng/ml**.

Ziprasidone

Ziprasidone is a derivative of piperazine. Its metabolism to 4 major metabolites occurs in the liver, with the participation of aldehyde oxidase, CYP3A4 and probably CYP1A2. Half-life varies depending on the route of administration – after oral or intravenous administration it is 6–7 hours, and after intramuscular administration – 8–10 hours. The average recommended daily dose is in the range of 120–160 mg. The advantage of a daily dose of 120 mg over lower doses has been demonstrated in a study by Mamo et al. [97], as the relationship of this dose with therapeutically beneficial 5HT2 receptor occupancy has been noticed. At the same time, a significant correlation between dose and D2/D3 receptors occupancy, and a slightly higher preference (about 10%) to these receptors in extrastriatal areas in relation to striatum has been proven [98].

In the literature, evidence of work on methods for monitoring concentrations of ziprasidone can be found, e.g., dried blood spot testing, microextraction by packed sorbent, mass spectrometry [99–102]. Little research on the plasma concentrations of ziprasidone was conducted. 2 studies on the pharmacokinetics of the drug were attended by 370 and 463 patients receiving daily doses of 20–320 mg. The achieved concentrations confirmed the previously proposed therapeutic range of **50–130 ng/ml** and the correlation of doses with concentrations [103, 104]. No substantial relationship of the occurrence of side effects and the concentration or dose was noticed. Lower concentrations were observed in smokers [104] and no effects of other drugs (i.a., armodafinil – also metabolized with the participation of CYP3A4) on concentrations of ziprasidone were recorded [104, 105].

To the observed inter – and intraindividual differences in the results of measurements of concentrations, therapeutic drug monitoring is considered useful in the case of ziprasidone.

Recapitulation

Utility of therapeutic drug monitoring has been proven for some typical (haloperidol, fluphenazine, perphenazine) and atypical (clozapine, olanzapine, risperidone) antipsychotics. In the case of drugs such as asenapine or the latest, as iloperidone,

perospirone, bifeprunox, lurasidone, brexpiprazole, or cariprazine there are no or still too few reports to determine the recommended concentration ranges.

All the research shows that TDM can be highly useful for avoiding an overdose resulting in the occurrence of adverse effects, including irreversible extrapyramidal symptoms, and, especially in the case of clozapine, also seizures. For patients, this essentially translates into quality of life [1]. An undoubted benefit of TDM is the safety of patients with the possibility to use the lowest doses that provide a satisfactory clinical effect [106]. In the case of antipsychotics, D2 receptor occupancy evaluated in PET or SPECT is an essential indicator of the efficacy of treatment. This correlates with the plasma concentration even more than dose [106]. In the AGNP studies, the effective and safe D2 receptor occupancy was established at 60–80% [1]. However, low availability of PET and SPECT in Poland due to financial and equipment limitations can be problematic. Therefore, there is no common practice of applying such imaging in TDM. It would be undoubtedly worthwhile to trace the financial benefits with the introduction of TDM in justified cases in the context of total costs of treatment, including the treatment of relapse and results of adverse effects. Estimation of the costs is not easy due to the lack of guidelines for the amount or frequency of measurements and the distinctness of each case. We could therefore talk about the price of a single test. Among the above-mentioned methods of measuring the plasma concentration of a drug, the cheapest and most commonly used in European countries and in the United States is the high-performance liquid chromatography (HPLC). According to European and American price lists, the price of a single measurement ranges from 50 to 80 PLN.

Studies suggest that the pharmacokinetics of certain drugs is characterized by large inter – and intraindividual differences (age, gender, lifestyle, genetic and metabolic characteristics, drug interactions), a narrow therapeutic range or non-linear dose-concentration ratio. All of these features provide the need and desirability of therapeutic drug monitoring for dose optimization. Baumann et al. [1] have proposed a kind of scale meant to illustrate the level of recommendations for TDM of individual drugs in clinical practice. Drugs discussed above and other atypical antipsychotics were included in this scale:

1. Strongly recommended – established therapeutic range (amisulpride, clozapine, olanzapine) and always when non-adherence is suspected.
2. Recommended – when suggested therapeutic ranges were obtained using therapeutically effective doses (aripiprazole, quetiapine, paliperidone, risperidone + 9-OH-risperidone, sertindole, ziprasidone).
3. Useful – when suggested therapeutic concentration ranges were obtained at doses in steady-state – after 4–5 $T_{1/2}$ of the drug (iloperidone, zotepine).
4. Probably useful – when suggested concentration ranges were obtained at therapeutic doses (asenapine).
5. Not recommended – unique pharmacology of a drug, e.g., irreversible blockade of an enzyme or flexible dosing according to clinical symptoms [96].

Table 2. **The level of recommendation for the use of TDM in combination with the doses and therapeutic concentrations of the discussed atypical antipsychotics**

Drug	Average oral therapeutic antipsychotic doses [mg/day]	Half–life [h]	Therapeutic plasma concentration range [ng/ml]	Level of recommendation for TDM
Amisulpride	300–800	12–20	200–320	1
Aripiprazole	15–30	60–146	150–210	2
Clozapine	200–600	6–26	350–500	1
Olanzapine	10–20	34	20–40	1
Quetiapine	200–600	7	50–500	2
Paliperidone	3–12	23–24	20–60	2
Risperidone/ 9-OH-risperidone	2–4	3/23–24	20–60	2
Sertindole	12–20	55–90	50–100	2
Ziprasidone	120–160	6–7	50–130	2

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